

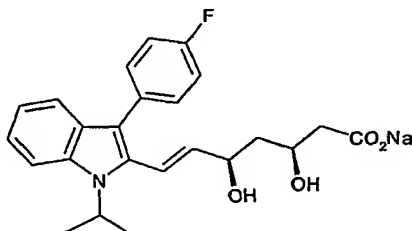
### Crystalline Form of Fluvastatin Sodium

The present invention is directed to novel crystalline form of Fluvastatin sodium, processes for the preparation and pharmaceutical compositions comprising this crystalline form.

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Fluvastatin sodium is known by its chemical name ( $\pm$ )-7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid monosodium salt. Fluvastatin sodium is a racemic mixture of the 3R,5S- and 3S,5R-dihydroxy enantiomers and has the following formula:

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Fluvastatin sodium is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) and is used to lower the blood cholesterol level.

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Fluvastatin sodium salt is disclosed in US-A-4,739,073. In this patent Fluvastatin sodium is obtained by lyophilization. WO-A-97/49681 and its US equivalent US-A-6,124,340 describe that lyophilization of Fluvastatin sodium yields a mixture of a crystalline form, designated as Form A, and amorphous material, and disclose a new crystalline form, designated as Form B. WO-A-03/13512 discloses 4 new crystalline hydrates, designated as Forms C, D, E and F. These crystalline hydrates have water contents which ranges from 3 to 32%. The stability of these new crystalline hydrates very much depend on the relative air humidity of the surrounding atmosphere. For example, Form D is the most stable crystalline form in atmospheres with an air humidity ranging from 30 to 50%, whereas Form F is stable in atmospheres with an air humidity of up to 90%. However, there is still a need for stable crystalline forms which can be used for example in gel or wet formulations.

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It has now been found that Fluvastatin sodium can surprisingly be prepared as a novel crystalline hydrate, which is stable in saturated aqueous environments. This novel crystalline

hydrate, herein designated as Form G, is a liquid crystalline material which, for example, allows gel or wet formulations of Fluvastatin sodium.

Thus the present invention provides the following novel crystalline form of Fluvastatin sodium:

A crystalline polymorph of  $(\pm)$ -7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid monosodium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å):

29.2 (w), 15.0 (vw), 10.1 (m), 7.6 (vs), 6.10 (s), 5.09 (m), 4.37 (s), 3.83 (w), 3.07 (m), herein designated as Form G. The abbreviations in brackets mean: (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity; (w) = weak intensity; and (vw) = very weak intensity. A characteristic X-ray powder diffraction pattern for Form G is depicted in Figure 1.

Furthermore, the present invention is directed to processes for the preparation of Form G. Form G of Fluvastatin sodium can generally be prepared from any crystalline Form or amorphous Fluvastatin sodium, or mixtures thereof, for example, by filtration of an aqueous suspension. The suspension may be obtained, for example, by introducing amorphous or any crystalline form of Fluvastatin sodium, e.g. form A, B, C, D, E or F, into water; usually, the amount of water used is insufficient to dissolve significant amounts of the material, e.g. by using the about 2 – 10 fold weight of water, relative to Fluvastatin sodium. It may also be obtained by crystallizing or partially crystallizing Fluvastatin sodium in water, e.g. by cooling of a solution or diluted suspension in water.

As a rule, the water content in the present Form G is 30% by weight or more. Small changes in the water content can cause small deviations in the d-values of characteristic peaks in the X-ray powder diffraction patterns.

Another object of the present invention are pharmaceutical compositions comprising an effective amount of crystalline polymorphic Form G, and a pharmaceutically acceptable carrier. The polymorphic form G may be used as a single component or as a mixture with other crystalline forms or the amorphous form of Fluvastatin sodium.

As to pharmaceutical compositions of Fluvastatin sodium it is preferred that these contain 25-100% by weight, especially 50-100% by weight, of Form G, based on the total amount of Fluvastatin sodium. Preferably, such an amount of Form G of Fluvastatin sodium is 75-100% by weight, especially 90-100% by weight. Highly preferred is an amount of 95-100% by weight.

The compositions of the invention include powders, granulates, aggregates and other solid compositions comprising crystalline polymorphic form G. In addition, the compositions that are contemplated by the present invention may further include diluents, such as

10 cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl, cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents like calcium carbonate and calcium diphosphate and other diluents known to the pharmaceutical industry.

15 Yet other suitable diluents include waxes, sugars and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin. Of special importance are aqueous gels or liquid formulations.

Further excipients that are within the contemplation of the present invention include binders,

20 such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes. Excipients that also may be present in the solid compositions further include disintegrants like sodium starch glycolate, croscopovidone, low-substituted hydroxypropyl cellulose and others. In addition, excipients may include tableting lubricants like magnesium and calcium stearate and sodium

25 stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration.

30 Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

Dosage forms include solid dosage forms, like tablets, powders, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions and elixirs. While the description is not intended to be limiting, the invention is also not intended to pertain to true solutions of Fluvastatin sodium whereupon the properties that distinguish the solid forms of  
5 Fluvastatin sodium are lost. However, the use of the novel forms to prepare such solutions is considered to be within the contemplation of the invention.

Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may  
10 be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be  
15 employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

Preferred unit dosages of the pharmaceutical compositions of this invention typically contain  
20 from 0.5 to 100 mg of the novel Fluvastatin sodium form or mixtures thereof with each other or other forms of Fluvastatin sodium. More usually, the combined weight of the Fluvastatin sodium forms of a unit dosage are from 2.5 mg to 80 mg, for example 5, 10, 20 or 40 mg.

The following Examples illustrate the invention in more detail. Temperatures are given in  
25 degrees Celsius. All percentages are given by weight if not otherwise indicated.

Example 1: Preparation of polymorphic Form G

300 mg of Fluvastatin sodium Form A are suspended in 1.0 ml water at ambient temperature. The resulting suspension is stirred for 18 hours. The solid residue is separated by filtration.  
30 Without any further drying, the obtained solid paste is investigated by powder X-ray diffraction in a closed sample chamber under an adjusted relative humidity of about 90% or higher. The X-ray powder diffraction pattern is depicted in Figure 1.

- 5 -

Exactly the same result is obtained when example 1 is repeated and the solid residue is filtered after only 15 minutes of stirring.

Also the same results are obtained when example 1 is repeated starting from any other crystalline form of Fluvastatin sodium.

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Brief description of the drawing

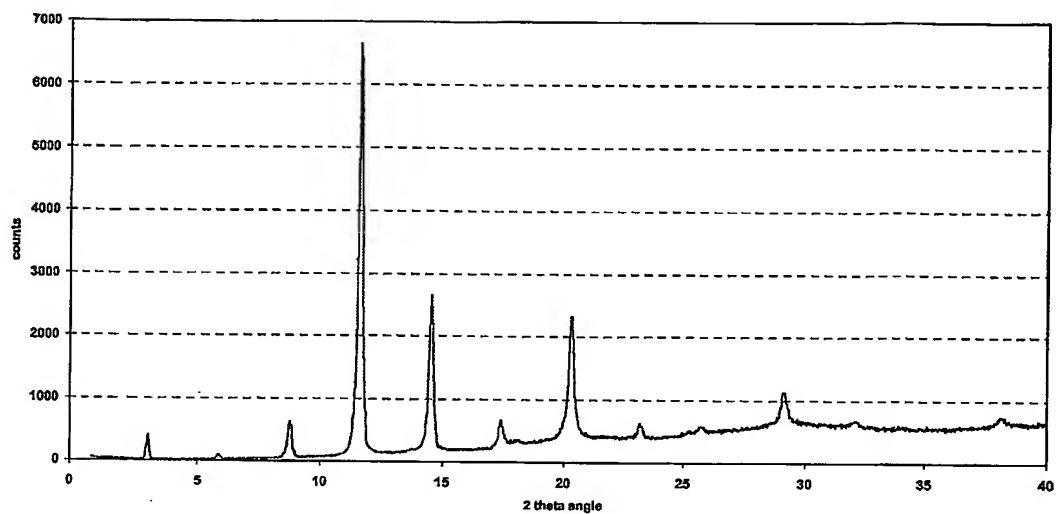
Figure 1 is a characteristic X-ray powder diffraction pattern for Form G.

Claims

1. A crystalline polymorph of ( $\pm$ )-7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid monosodium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values ( $\text{\AA}$ ): 7.6 (vs), 6.10 (s), and 4.37 (s), wherein (vs) = very strong intensity and (s) = strong intensity.
2. A crystalline polymorph of ( $\pm$ )-7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid monosodium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values ( $\text{\AA}$ ): 10.1 (m), 7.6 (vs), 6.10 (s), 5.09(m), 4.37 (s) and 3.07(m), wherein (vs) = very strong intensity, (s) = strong intensity and (m) = medium intensity.
3. A crystalline polymorph of ( $\pm$ )-7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid monosodium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values ( $\text{\AA}$ ): 29.2 (w), 15.0 (vw), 10.1 (m), 7.6 (vs), 6.10 (s), 5.09(m), 4.37 (s), 3.83 (w) and 3.07(m), wherein (vs) = very strong intensity, (s) = strong intensity, (m) = medium intensity, (w) = weak intensity and (vw) = very weak intensity.
4. A process for the preparation of a crystalline polymorph according to claims 1 to 3, wherein Fluvastatin sodium is filtered off from an aqueous suspension.
5. A process according to claim 4 for in which the aqueous suspension is prepared from any of the known crystalline forms or the amorphous form of Forms of Fluvastatin sodium.
6. A process according to claim 4 or 5 in which an aqueous suspension of Fluvastatin sodium is stirred before filtration.
7. A pharmaceutical composition comprising an effective amount of a crystalline polymorphic form according to any of claims 1 to 3 and a pharmaceutically acceptable carrier.

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Fig. 1

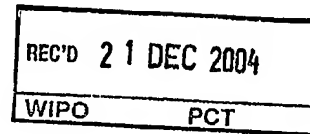




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Klybeckstrasse 141  
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SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.  
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Crystalline Form of Fluvastatin Sodium

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)  
revendiquée(s)

Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

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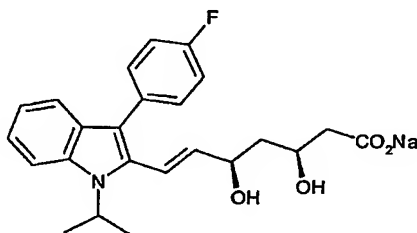
Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of  
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PT RO SE SI SK TR LI

### Crystalline Form of Fluvastatin Sodium

The present invention is directed to novel crystalline form of Fluvastatin sodium, processes for the preparation and pharmaceutical compositions comprising this crystalline form.

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Fluvastatin sodium is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) and is used to lower the blood cholesterol level.

Fluvastatin sodium salt is disclosed in US-A-4,739,073. In this patent Fluvastatin sodium is obtained by lyophilization. WO-A-97/49681 and its US equivalent US-A-6,124,340 describe that lyophilization of Fluvastatin sodium yields a mixture of a crystalline form, designated as Form A, and amorphous material, and disclose a new crystalline form, designated as Form B. WO-A-03/13512 discloses 4 new crystalline hydrates, designated as Forms C, D, E and F. These crystalline hydrates have water contents which ranges from 3 to 32%. The stability of these new crystalline hydrates very much depend on the relative air humidity of the surrounding atmosphere. For example, Form D is the most stable crystalline form in atmospheres with an air humidity ranging from 30 to 50%, whereas Form F is stable in atmospheres with an air humidity of up to 90%. However, there is still a need for stable crystalline forms which can be used for example in gel or wet formulations.

We now have found that Fluvastatin sodium can surprisingly be prepared as a novel crystalline hydrate, which is stable in saturated aqueous environments. This novel crystalline hydrate, herein designated as Form G, is a liquid crystalline material which, for example, allows gel or wet formulations of Fluvastatin sodium.

Thus the present invention provides the following novel crystalline form of Fluvastatin sodium:

A crystalline polymorph of  $(\pm)$ -7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid monosodium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å): 29.2 (w), 15.0 (vw), 10.1 (m), 7.6 (vs), 6.10 (s), 5.09 (m), 4.37 (s), 3.83 (w), 3.07 (m), herein designated as Form G. The abbreviations in brackets mean: (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity; (w) = weak intensity; and (vw) = very weak intensity. A characteristic X-ray powder diffraction pattern for Form G is depicted in Figure 1.

Furthermore, the present invention is directed to processes for the preparation of Form G.

Form G of Fluvastatin sodium can generally be prepared from any crystalline Form or amorphous Fluvastatin sodium, or mixtures thereof, for example, by filtration of an aqueous suspension. As a rule the estimated water content is >30%.

Small changes in the water content can cause small deviations in the d-values of characteristic peaks in the X-ray powder diffraction patterns.

Another object of the present invention are pharmaceutical compositions comprising an effective amount of crystalline polymorphic Form G, and a pharmaceutically acceptable carrier. The polymorphic form G may be used as a single component or as a mixture with other crystalline forms or the amorphous form of Fluvastatin sodium.

As to pharmaceutical compositions of Fluvastatin sodium it is preferred that these contain 25-100% by weight, especially 50-100% by weight, of Form G, based on the total amount of

Fluvastatin sodium. Preferably, such an amount of Form G of Fluvastatin sodium is 75-100% by weight, especially 90-100% by weight. Highly preferred is an amount of 95-100% by weight.

The compositions of the invention include powders, granulates, aggregates and other solid compositions comprising crystalline polymorphic form G. In addition, the compositions that are contemplated by the present invention may further include diluents, such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl, cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents like calcium carbonate and calcium diphosphate and other diluents known to the pharmaceutical industry. Yet other suitable diluents include waxes, sugars and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin. Of special importance are aqueous gels or liquid formulations.

Further excipients that are within the contemplation of the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes. Excipients that also may be present in the solid compositions further include disintegrants like sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others. In addition, excipients may include tableting lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

Dosage forms include solid dosage forms, like tablets, powders, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions and elixirs. While the description is not intended to be limiting, the invention is also not intended to pertain to true solutions of Fluvastatin sodium whereupon the properties that distinguish the solid forms of Fluvastatin sodium are lost. However, the use of the novel forms to prepare such solutions is considered to be within the contemplation of the invention.

Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

Preferred unit dosages of the pharmaceutical compositions of this invention typically contain from 0.5 to 100 mg of the novel Fluvastatin sodium form or mixtures thereof with each other or other forms of Fluvastatin sodium. More usually, the combined weight of the Fluvastatin sodium forms of a unit dosage are from 2.5 mg to 80 mg, for example 5, 10, 20 or 40 mg.

The following Examples illustrate the invention in more detail. Temperatures are given in degrees Celsius.

#### Example 1: Preparation of polymorphic Form G

300 mg of Fluvastatin sodium Form A are suspended in 1.0 ml water at ambient temperature. The resulting suspension is stirred for 18 hours. The solid residue is separated by filtration. Without any further drying the obtained solid paste is investigated by powder X-ray diffraction in a closed sample chamber under an adjusted relative humidity of about 90% or higher. The X-ray powder diffraction pattern is depicted in Figure 1.

Exactly the same result is obtained when example 1 is repeated and the solid residue is filtered after only 15 minutes of stirring.

Also the same results are obtained when example 1 is repeated starting from any other crystalline form of Fluvastatin sodium.

Brief description of the drawing

Figure 1 is a characteristic X-ray powder diffraction pattern for Form G.

Claims

1. A crystalline polymorph of  $(\pm)$ -7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid monosodium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å): 7.6 (vs), 6.10 (s), and 4.37 (s), wherein (vs) = very strong intensity and (s) = strong intensity.
2. A crystalline polymorph of  $(\pm)$ -7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid monosodium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å): 10.1 (m), 7.6 (vs), 6.10 (s), 5.09(m), 4.37 (s) and 3.07(m), wherein (vs) = very strong intensity, (s) = strong intensity and (m) = medium intensity.
3. A crystalline polymorph of  $(\pm)$ -7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid monosodium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å): 29.2 (w), 15.0 (vw), 10.1 (m), 7.6 (vs), 6.10 (s), 5.09(m), 4.37 (s), 3.83 (w) and 3.07(m), wherein (vs) = very strong intensity, (s) = strong intensity, (m) = medium intensity, (w) = weak intensity and (vw) = very weak intensity.
4. A process for the preparation of a crystalline polymorph according to claims 1 to 3, wherein Fluvastatin sodium is filtered off from an aqueous suspension.
5. A process according to claim 4 for in which the aqueous suspension is prepared from any of the known crystalline forms or the amorphous form of Forms of Fluvastatin sodium.
6. A process according to claim 4 or 5 in which an aqueous suspension of Fluvastatin sodium is stirred before filtration.

7. A pharmaceutical composition comprising an effective amount of a crystalline polymorphic form according to any of claims 1 to 3 and a pharmaceutically acceptable carrier.
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**Abstract**

A novel crystalline form of Fluvastatin sodium hydrate is described, referred to hereinafter as polymorphic Form G. Furthermore, processes for the preparation of this crystalline form and pharmaceutical compositions comprising this crystalline form are reported.